National Pharmaceutical Control Bureau
Ministry of Health Malaysia

WHO Collaborating Centre
For Regulatory Control of Pharmaceuticals

Member of Pharmaceutical
Inspection Cooperation Scheme

Non-OECD member with
full adherent to MAD system in
Assessment of Chemicals

MS ISO 9001:2008 Certified
MS ISO/IEC 17025 Accredited

STRENGTHENING OF REGULATORY OVERSIGHT IN VACCINES

National Regulatory Conference
4 – 6th August 2015

NOORUL AKMAR MOHD NUR
Center for Quality Control
National Pharmaceutical Control Bureau,
Ministry of Health Malaysia

PRESENTATION OUTLINE

- The importance of Vaccine Lot Release
- Vaccine Lot Release (VLR)
- Scope of Vaccine Lot Release
- Milestones of the implementation
- Guidelines for VLR in Malaysia
- Process flow of VLR
- Examples of Certificates & Notification issued by NPCB
- Statistics
- Pre and post – implementation of VLR
- Challenges in implementation
- Way forward

THE IMPORTANCE OF VACCINE LOT RELEASE

PRODUCT CHARACTERISTIC

- Biologics has large and complex structure
- Biological molecules cannot be heat-sterilized, therefore aseptic manufacturing is a must to preclude contamination
- Biologics are unstable and sensitive to temperature. Therefore storage in proper condition should be monitored

PUBLIC SAFETY

- Vaccines are used in healthy populations, especially infants.
- Safety issues with a particular lot may not be known immediately after administration
- Vaccine quality have a direct impact on the public acceptance of immunization programmes, thus potentially compromising public health strategies.

VACCINE LOT RELEASE (VLR)

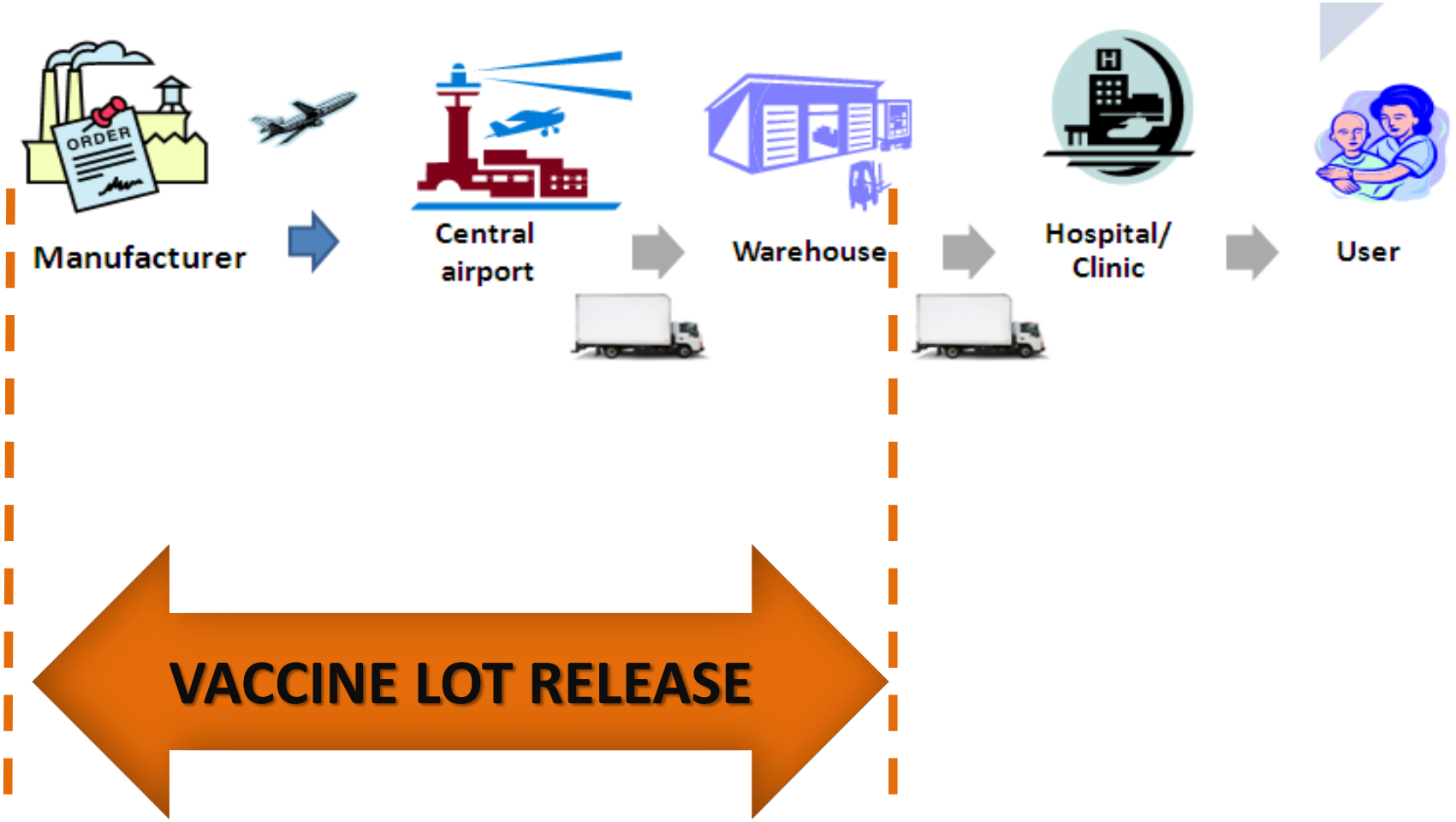
According to Guidelines by World Health Organization (WHO)

- Review of manufacturers' summary protocols, which include manufacturing and testing data for each manufactured lot of the product
- Recognition/ acceptance of lot release certificate from responsible National Regulatory Authority
- Independent testing of the manufacturers' quality control testing by the National Control Laboratory

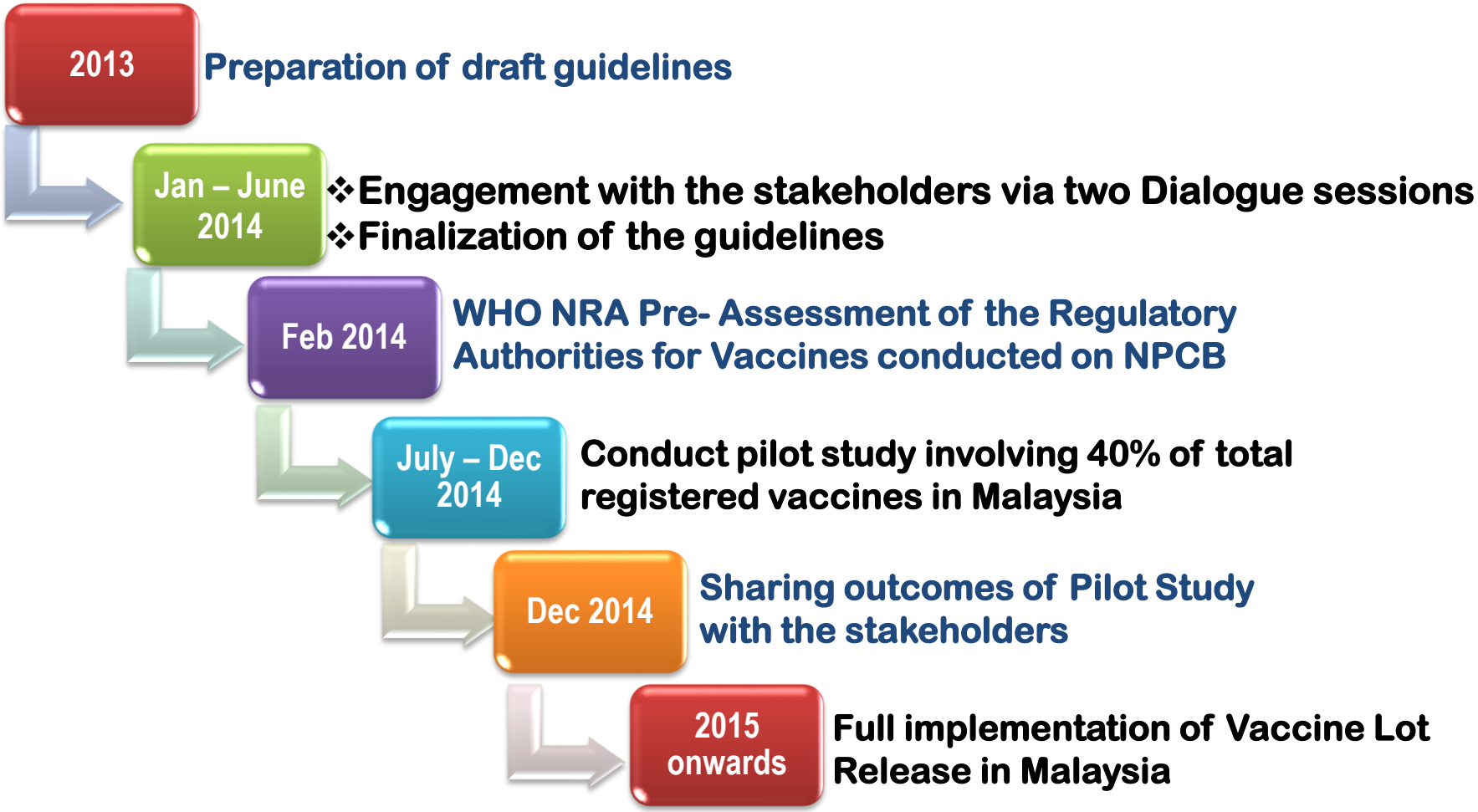
Vaccine Lot Release in Malaysia

- Review of manufacturer's summary protocols based on product dossier which has been approved by NPCB during product registration
- Review of cold chain system monitoring

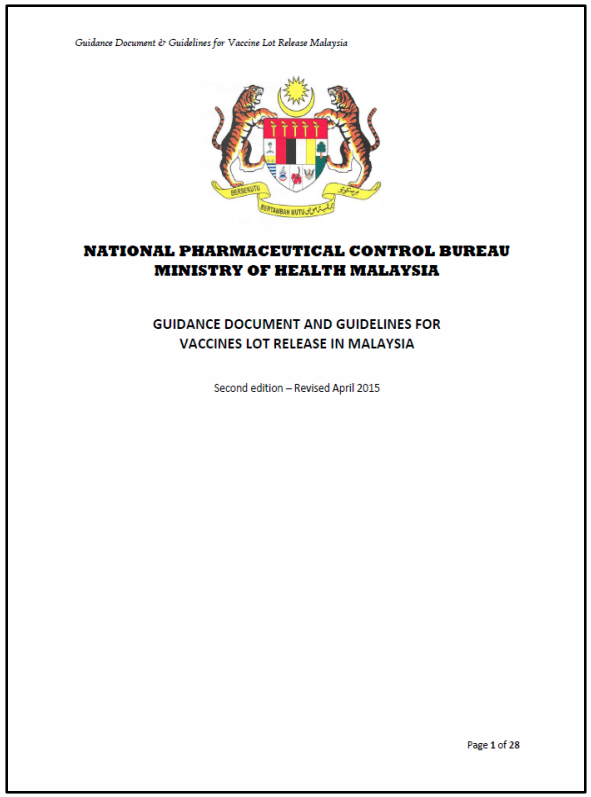
SCOPE OF VLR


ORDER
Manufacturer
Central airport
Warehouse
Hospital/ Clinic
User
VACCINE LOT RELEASE

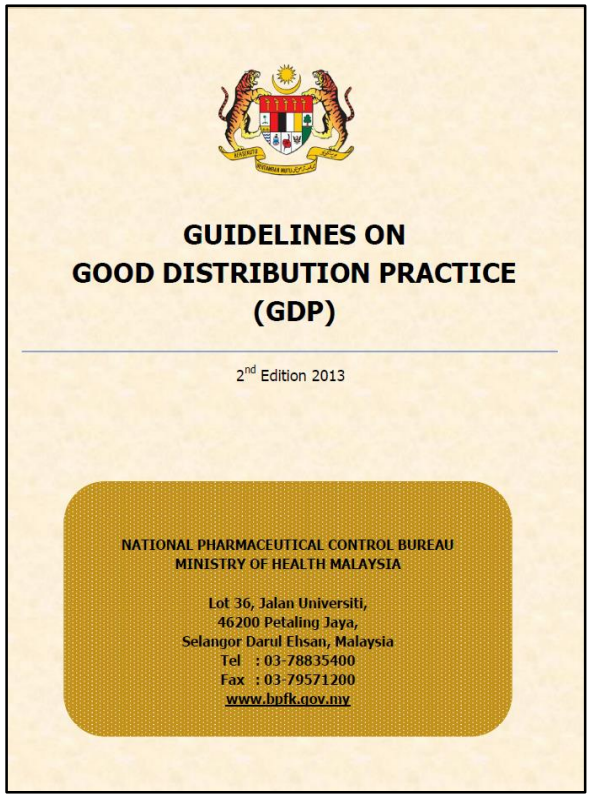
MILESTONES OF THE IMPLEMENTATION



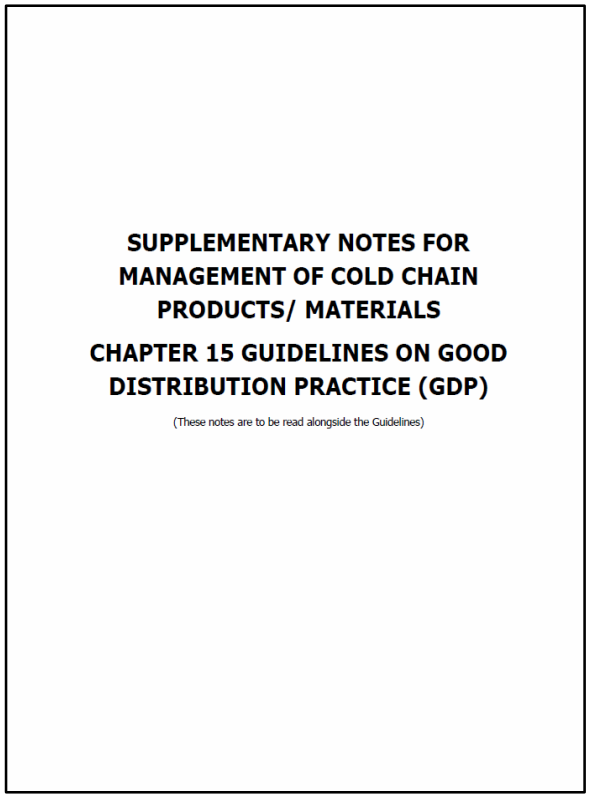
GUIDELINES FOR VLR IN MALAYSIA



Guidance Document and Guidelines for Vaccine Lot Release in Malaysia, 2nd edition April 2015

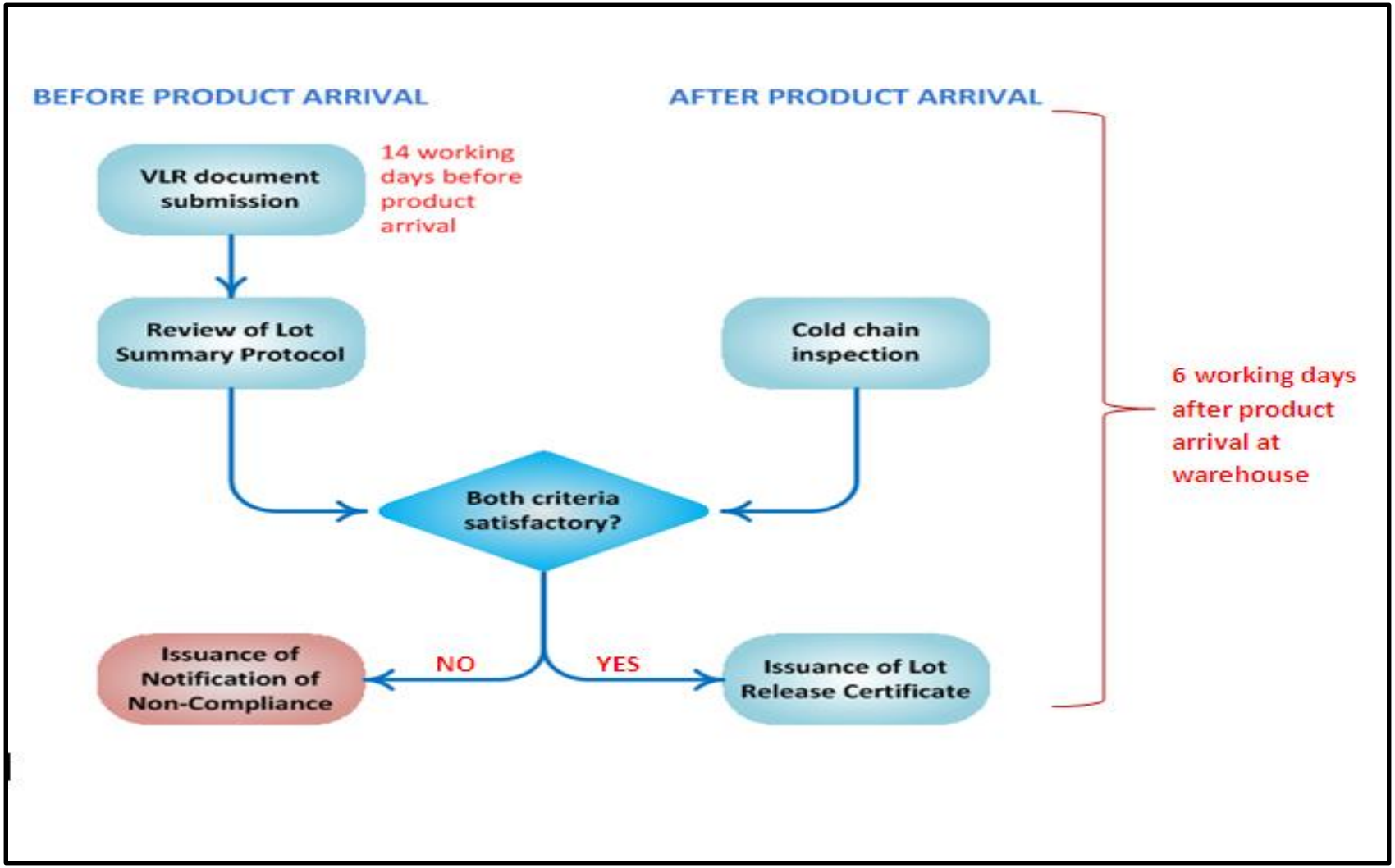


Guidelines on Good Distribution Practice (GDP) 2nd edition 2013



Supplementary Noted for Management of Cold Chain Products/Materials, Chapter 15 GDP

PROCESS FLOW OF VLR



CERTIFICATES & NOTIFICATION

Lot Release Certificate

CERTIFICATE FOR THE RELEASE

Certificate no: LRC0145/2015

The following lot of [redacted] produced by [redacted], whose numbers appears on the labels of the final containers, meets the national requirements for lot release and conforms to the approved specifications.

As a minimum, this certificate is based on examination of the manufacturing protocol.

Lot No	Expiry date	No. of doses	No. of doses per container
[redacted]	28 February 2018	33,272	1

Signature:

Name of authorized person: DR TAJUDDIN AKASAH
Head of Centre for Quality Control
for Director of Pharmacy Regulatory
National Pharmaceutical Control Bureau
Ministry of Health Malaysia

Date: 21 July 2015

Notification of Non-Compliance

Date of issuance: 17 December 2014

NOTIFICATION OF NON-COMPLIANCE

Notification no: NNC 0005/2014

The following lot of [redacted] produced by [redacted] whose numbers appear on the labels of the final containers, **DOES NOT MEET** the requirements as below:

- [x] National requirement on Good Distribution Practice for Cold Chain
- [ ] National requirement on Lot Summary Protocol Evaluation
- [x] Requirements for Hepatitis B Vaccines Made by Recombinant DNA Technology, WHO Technical Report Series, No. 786, 1989, Annex 2

Lot No	Expiry date	No. of containers	No. of doses per container
[redacted]	11 September 2017	154,460	1

Signature:

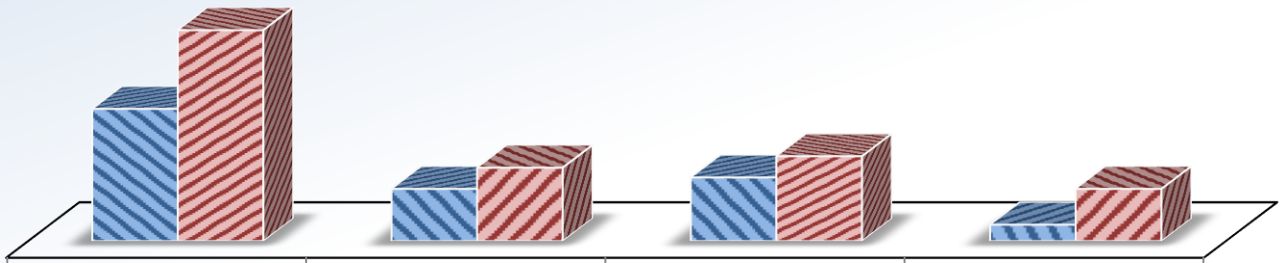
Name of authorized person: Ms. TAN JEEN LING
Director for Pharmacy Regulatory
National Pharmaceutical Control Bureau
Ministry of Health Malaysia

Signature: 17 December 2014

All the certificates and notifications issued by NPCB to the Product Registration Holder could be viewed from NPCB's website: http://www.bpfk.gov.my

STATISTICS 1 (July 2014 – June 2015)

No. of Vaccine Lot Release application received

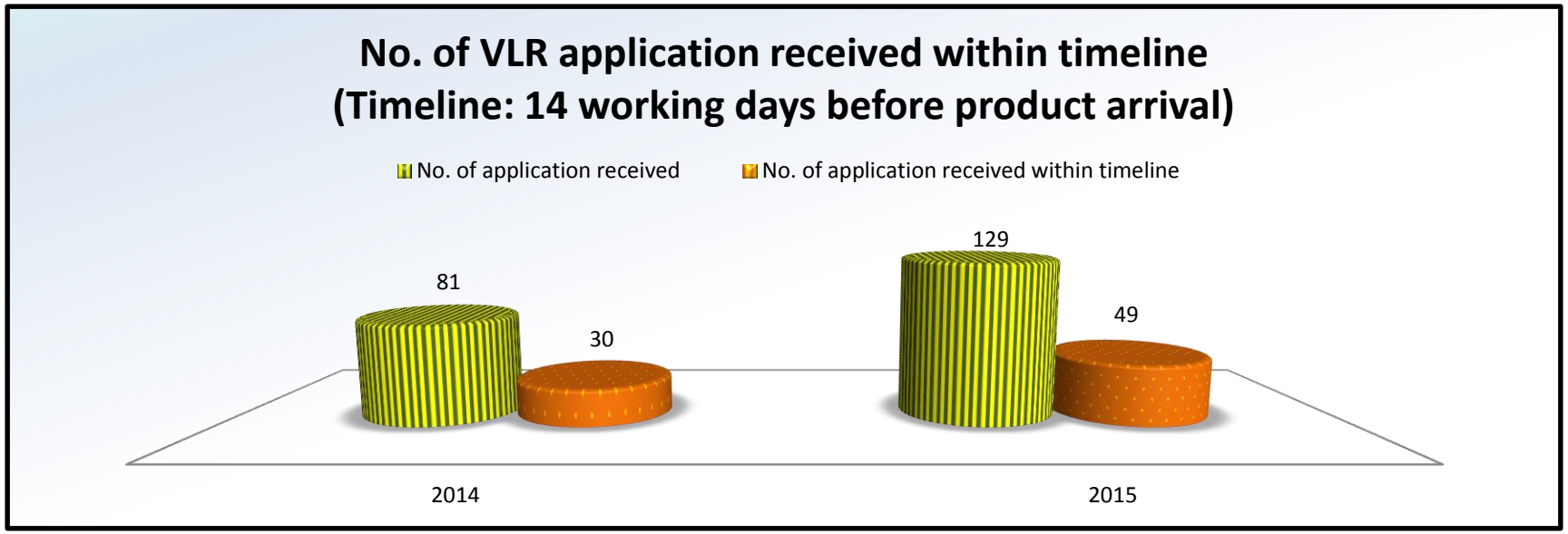


	Total application received	Combination vaccine	Monovalent vaccine	Polyvalent vaccine
2014	81	32	39	10
2015	129	45	52	32

During Pilot Study (July – December 2014), there were 81 applications received involving BCG, HepB, Hib, Diphteria, Pertussis, Tetanus, Polio and HPV vaccine either as combination vaccine or as single antigen.

Starting from January 2015, Vaccine Lot Release has been implemented to all registered imported vaccine. The number of application increase by 59% and monovalent vaccines continue to be the highest imported type of vaccine.

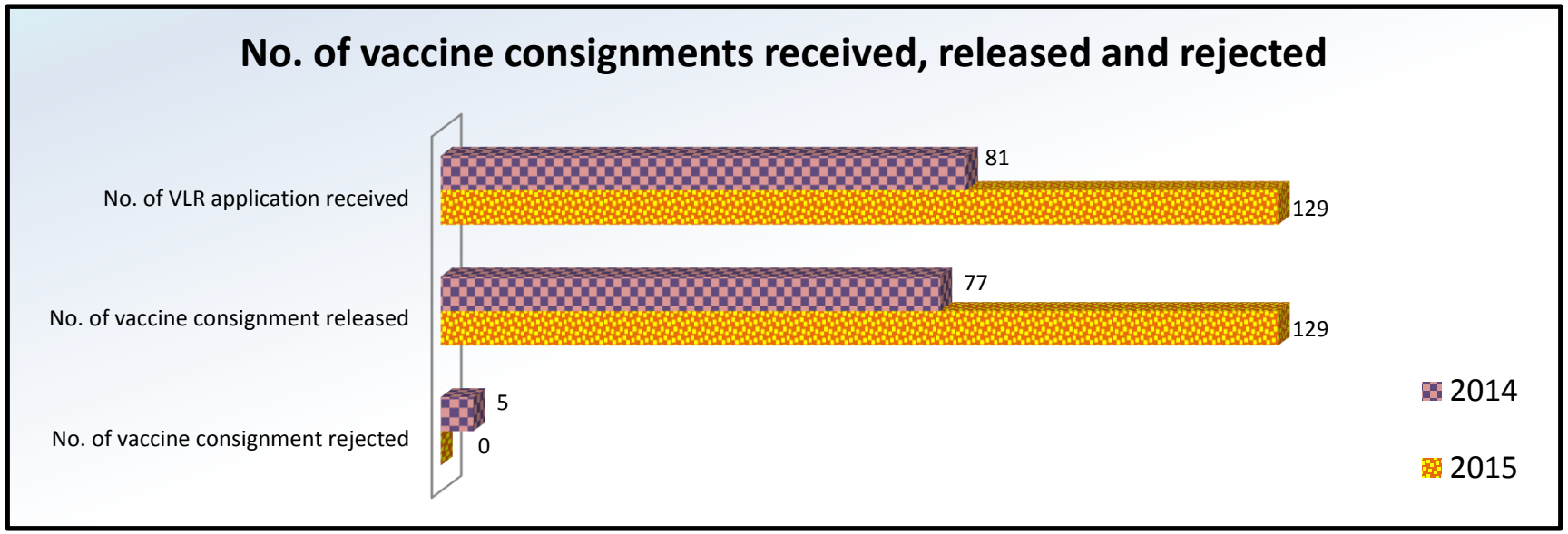
STATISTICS 2 (July 2014 – June 2015)



One of the challenges faced by NPCB in implementing VLR is poor compliance with submission's timeline. During the Pilot Study, 37% of applications (30 out of 81) were submitted within the timeline where as in 2015, there is a negligible improvement with 38% of applications (49 out of 129) were submitted within 14 working days before product arrival

Poor compliance with submission's timeline affects the plan for lot summary protocol review and schedule for cold chain inspection.

STATISTICS 3 (July 2014 – June 2015)



There were a total of 81 applications received in 2014 and 5 consignments were rejected. 1 of the 5 consignments were partially released and rejected due to some of the vaccines found to be frozen during cold chain inspection. Meanwhile the other 4 consignments were rejected due to temperature excursion more than 8°C without supporting evidence in ensuring the cold chain monitoring.

For 129 applications received in 2015, all the vaccine consignments have been released.

STATISTICS 4 (July 2014 – June 2015)

Year	No. of release certificate issued within timeline	No. of release certificate issued > 6 working days	Percentage of delay in release
2014	65	12	18%
2015	120	9	7.5%

The statistics showed a reduction in percentage of delay in issuance of lot release certificate from 18% to 7.5%. The common reasons for the delay include:

1) Late submission of application
2) Re-dressing is conducted without NPCB's approval
3) Delay in providing feedback such as explanation of inconsistent information on the manufacturer's address and the reason of using inactivated electronic device during shipment.
4) Shake test needs to be conducted on suspected frozen vaccine

PRE & POST-IMPLEMENTATION (1)

FINDINGS DURING PILOT STUDY	POST-IMPLEMENTATION OF VLR
Electronic temperature device was not included in each shipping cartons	Electronic temperature device has been included in each shipping cartons. However new incidents were found: 1) Expired data logger was used during transportation 2) Some data logger was not activated 3) Incomplete data logger temperature recording
Poor planning on vaccine arrival time resulting cold chain inspectors waiting at warehouse	Still occurring

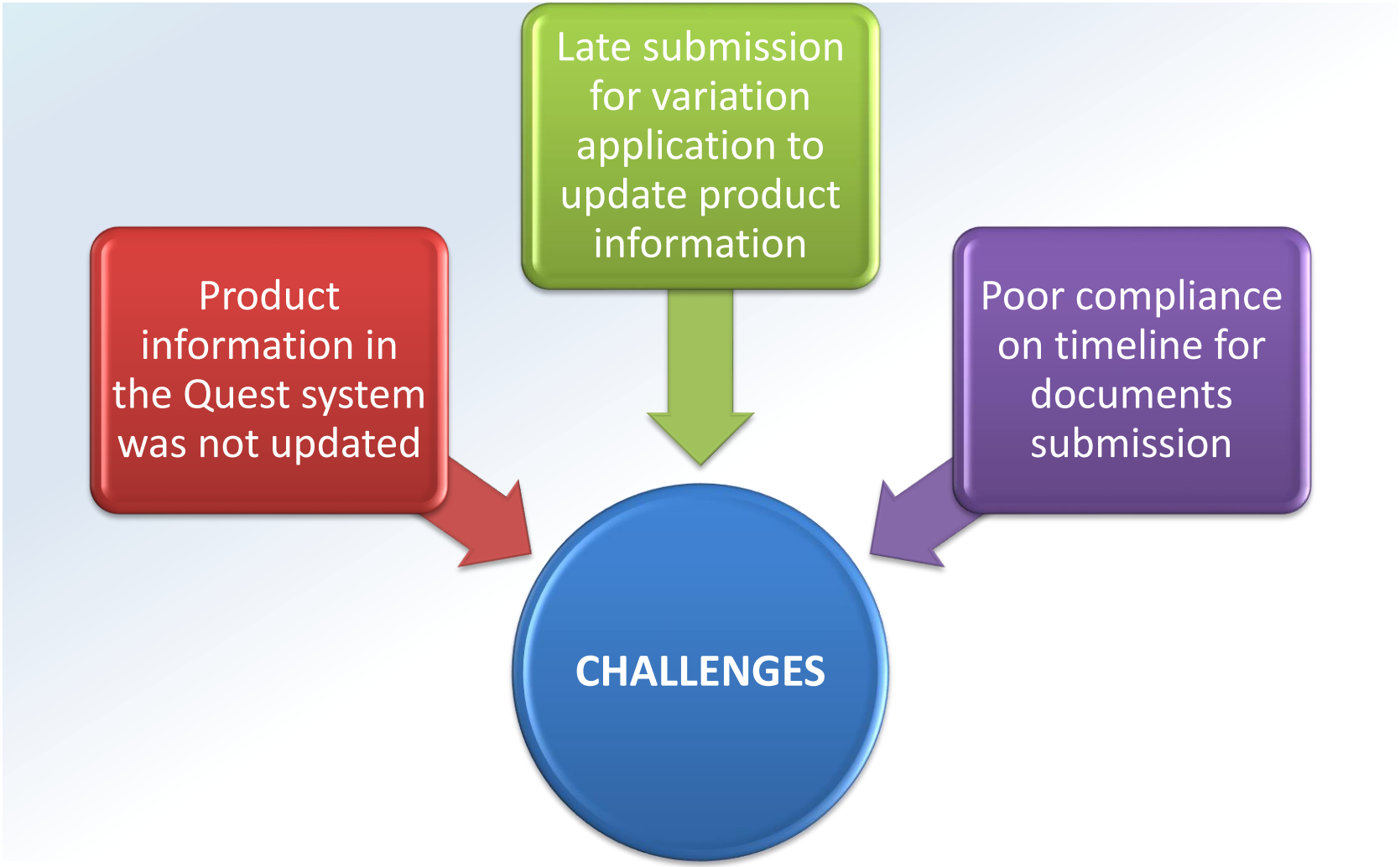
PRE & POST-IMPLEMENTATION (2)

FINDINGS DURING PILOT STUDY	POST-IMPLEMENTATION OF VLR
Temperature excursion	Still occurring but with supporting document
Unseal vaccine consignment without the presence of CC inspector	No incident
Transportation and packaging validation to support temperature excursion were not submitted	All transportation and packing validation were received by NPCB
Cold Chain Monitoring (CCM) card is used with gel/water ice pack during international shipping	CCM card is used only with dried ice international shipping

PRE & POST-IMPLEMENTATION (3)

FINDINGS DURING PILOT STUDY	POST-IMPLEMENTATION OF VLR
Poor compliance on timeline for documents submission	No improvement
Product information in Quest system was not updated	Increase in number of product variation application after raising of queries during review of lot summary protocol.
Testing methods and testing specifications in Quest system was not updated	
Inconsistent information on the manufacturer's address	Similar problem occurred for vaccines that were not involved in the Pilot Study
Deviation in vaccine quantity stated in VLR application form	

CHALLENGES IN IMPLEMENTATION (1)



CHALLENGES IN IMPLEMENTATION (2)

Increase number of importation via Exceptional Case Procedure

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4 applications in 2014 → 17 in 2015

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Priority review & urgent release to overcome critical shortage in hospital/clinics

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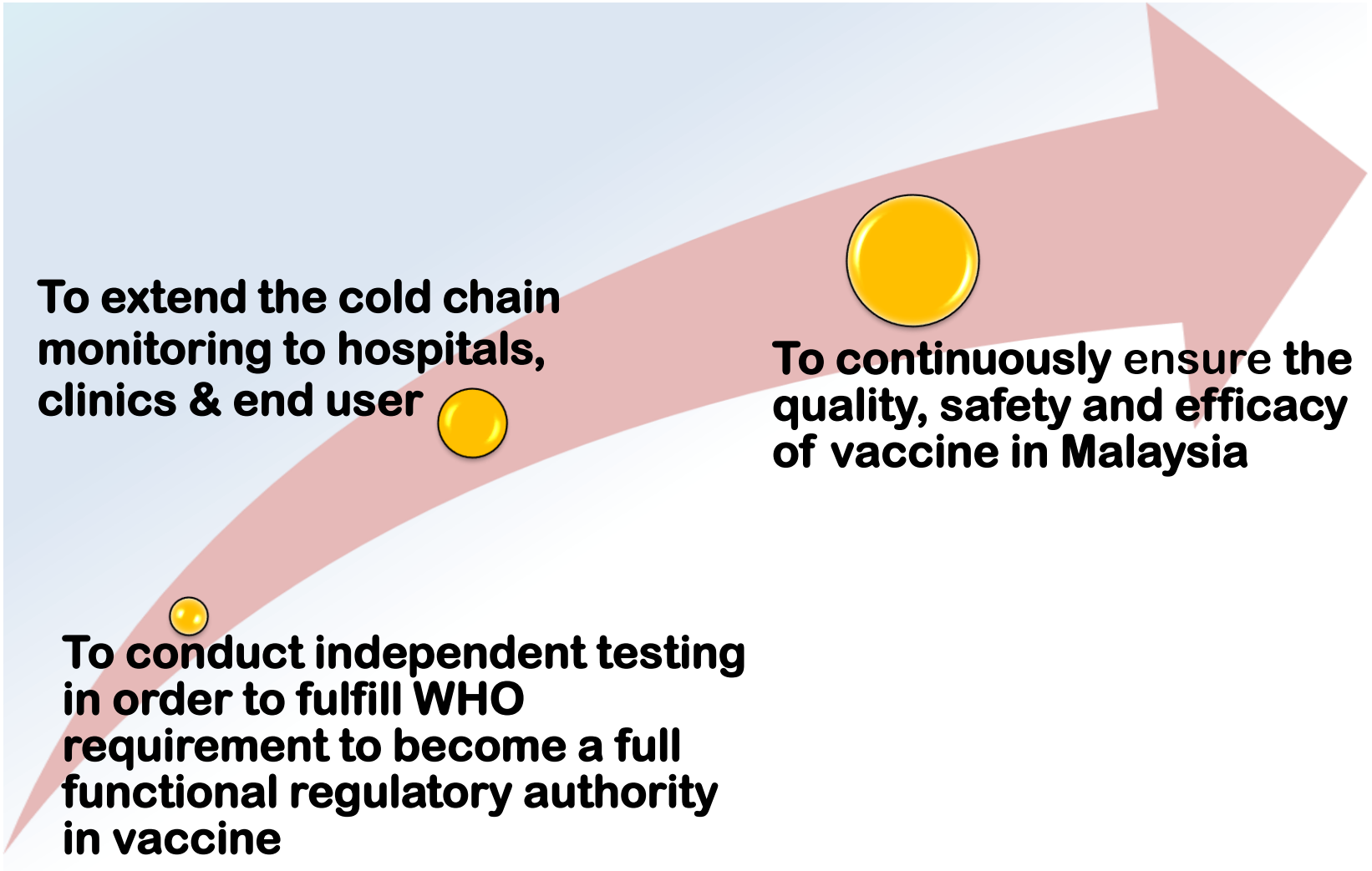
POOR STOCK MANAGEMENT ?

WAY FORWARD


To extend the cold chain monitoring to hospitals, clinics & end user
To continuously ensure the quality, safety and efficacy of vaccine in Malaysia
To conduct independent testing in order to fulfill WHO requirement to become a full functional regulatory authority in vaccine

ACKNOWLEDGEMENT

Director of NPCB
Deputy Directors of NPCB
Members of Task Force Biological Lot Release and other government agencies

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THANK YOU
FOR YOUR ATTENTION

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